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ORIGINAL INVESTIGATION

Mutations in Fanconi anemia genes and the risk of esophageal cancer

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Abstract The incidence of esophageal squamous cell carcinoma (ESCC) is very high in northeastern Iran. Previously, we reported a strong familial component of ESCC among Turkmens, who constitute approximately one-half of the population of this region. We hypothesized that the genes which cause Fanconi anemia might be candidate genes for ESCC. We sequenced the entire coding regions of 12 Fanconi anemia genes in the germline DNA of 190 Turkmen cases of ESCC. We identified three heterozygous insertion/deletion mutations: one in *FANCD2* (p.Val1233-del), one in *FANCE* (p.Val311SerfsX2), and one in *FANCL* (p.Thr367AsnfsX13). All three patients had a strong family history of ESCC. In addition, four patients (out of 746 tested) were homozygous for the *FANCA* p.Ser858Arg mutation, compared to none of 1,373 matched controls (OR = 16.7, 95% CI = 6.2–44.2, $P = 0.01$). The p. Lys3326X mutation in *BRCA2* (also known as Fanconi anemia gene *FANCD1*) was present in 27 of 746 ESCC cases and in 16 of 1,373 controls (OR = 3.38, 95% CI = 1.97–6.91, $P = 0.0002$). In summary, both heterozygous and homozygous mutations in several Fanconi anemia-predisposing genes are associated with an increased risk of ESCC in Iran.

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Introduction

Esophageal cancer is the eighth most common cancer in the world and is a significant global health problem (Parkin et al. 2005). The 5-year survival rate for patients with esophageal cancer is 10–16% (Parkin et al. 2005). A region in northeastern Iran at the Caspian Sea littoral has a very high incidence of esophageal cancer (Saidi et al. 2000; Semnani et al. 2006), most of which are squamous cell carcinomas. Previously, we reported a strong familial component of esophageal squamous cell carcinoma (ESCC) among Turkmen (Akbari et al. 2006). Turkmens constitute one-half of the population in this region. The lifetime risk of cancer was 14% for all individuals in the population and was 34% for those with a first-degree relative with esophageal cancer (HR = 2.3, 95% CI = 1.7–3.1, $P = 3 \times 10^{-8}$).